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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/088,502	03/28/2002	AKIRA MORIGUCHI	221045US0PCT	2405

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EXAMINER	
SWOPE, SHERIDAN	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 10/25/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/088,502	MORIGUCHI ET AL.	
	Examiner	Art Unit	
	Sheridan L. Swope	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 August 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6-15 and 18-26* is/are pending in the application.

4a) Of the above claim(s) *1-4,6,7 and 9-15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8 and 18-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response of August 4, 2004 to the First Action on the Merits of this case is acknowledged. It is acknowledged that Applicants have cancelled Claims 2, 3, 5, 16, and 17, amended Claims 8 and 18-20, and added Claims 21-26. Claims 1-4, 6-15, and 18-26 are pending. Claims 1, 4, 6, 7, and 9-15 stand withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected Inventions, there being no allowable generic or linking claim. Claims 8 and 18-26 are hereby examined.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Rejection of Claims 8 and 18-20 under 35 U.S.C. 103(a) as being unpatentable over NINDS, 1995 in view of Bundick et al, 1992 (IDS) and Mori et al, 1997 and further in view of Sharkey et al, 1994 or Kelly et al, 1997 (IDS) as evidenced by Steiner et al, 1998, for the reasons described in the prior action, is maintained.

In support of their request that said rejection be withdrawn, Applicants provide the following arguments.

1) NINDS, 1995 do not teach combination therapy with t-PA and an IL-2 inhibitor. Even if Bundick et al and Mori et al disclose FK506 is an IL-2 inhibitor and even if Sharkey et al and Kelley disclose that FK506 has neuroprotective activity, this is of no import because none of said teachings cure the deficiencies of NINDS.

2) While Steiner et al refers to combination therapy, there is no reference to FK506.

3) Steiner et al refers to a "number of problems" (Abstract) with respect to combination therapy.

4) Referring to neuroprotective and cytoprotective drugs, Steiner et al indicates that only a few have shown positive clinical results (pg 2, right column, parg 2) and that various trials have been abandoned or terminated (Table 1).

5) Steiner et al merely speculate that combination therapy with thrombolytic and neuroprotective agents may provide additional benefits and does not lead one of skill to administer effective amounts of both t-PA and tacrolimus.

6) The showing in the instant application of a synergistic effect of FK506 and t-PA further evidence the non-obviousness of the claimed invention.

These arguments are not found to be persuasive for the following reasons.

1) It is acknowledged that NINDS, 1995 do not teach combination therapy with t-PA and an IL-2 inhibitor. However, no single reference is required to teach said therapy, as this is a rejection under 35 U.S.C. § 103(a), not 35 U.S.C. § 102. The reasons Bundick et al, Mori et al, Sharkey et al and Kelley et al cure the deficiencies of NINDS are explained in the prior action. In summary, the NINDS teach treatment with t-PA for ischemic stroke but do not teach combination therapy with t-PA and an IL-2 inhibitor. The combination of Bundick et al, Mori et al, Sharkey et al and Kelley et al teach that FK506 is an IL-2 inhibitor that provides neuroprotection. Since, Steiner et al teach that combination therapy with thrombolytic and neuroprotective agents may provide additional benefits to those that can be achieved using an

individual agent alone, one of skill would be motivated to treat cerebral ischemia with the combination of t-PA and FK506.

2) It is acknowledged that Steiner et al do not specifically disclose FK506 in combination therapy. However, Steiner et al do teach combination therapy using thrombolytic neuroprotective agents (Title; Abstract, line 5-7; pg 5, parg 6 to pg 6, parg 5). In fact, the purpose of the publication of Steiner et al was to review the state of the art for combination therapy using neuroprotectants and thrombolytics in ischaemic stroke (Title). Although Steiner et al do not mention FK506, it was well known in the art that FK506 is a neuroprotectant (Sharkey et al or Kelley et al).

3) The problems referred to in the Abstract by Steiner et al are problems with clinical trial design and statistical analysis, not combination therapy per se (also see pg 6, parg 6-8).

4) It is acknowledged that only a limited number of individual neuroprotective drugs have shown positive clinical results. However, using neuroprotectants that are effective (e.g. tirilazad, a pan glutamate receptor antagonist, an NMDA receptor antagonist, an AMPA receptor antagonist, anti-ICAM-1, or nimodipine), Steiner et al clearly state that for stroke, the beneficial effects of combination therapy with neuroprotective and thrombolytic agents have already been shown in several animal studies (pg 6, parg 4).

5) The statement by Steiner et al that "The beneficial effects of combination therapy with neuroprotective and thrombolytic agents in stroke have already been shown in several animal studies" is not speculative. Furthermore, others also teach combination therapy with neuroprotective and thrombolytic agents (Hantson et al, 1997). Although Steiner et al do not

specifically mention the combination of the agents t-PA and tacrolimus, it is known in the art that said agents are thrombolytic and neurprotective, respectively (see (2) above).

6) The a synergistic effect of FK506 and t-PA do not render the instant invention non-obvious to a person of ordinary skill in the art, because Steiner et al clearly state that thrombolytic and neuroprotective agents may act synergistically (pg 5, parg 7). Furthermore, others have shown the synergistic effects of combined treatment with a neuroprotectant and a thrombolytic (Zivin et al, 1991, Table 1; Meden et al, 1993, Table 2 cols 11 & 13).

Therefore, Rejection of Claims 8 and 18-20 under 35 U.S.C. 103(a) as being unpatentable over NINDS, 1995 in view of Bundick et al, 1992 (IDS) and Mori et al, 1997 and further in view of Sharkey et al, 1994 or Kelly et al, 1997 (IDS) as evidenced by Steiner et al, 1998, for the reasons described in the prior action, is maintained.

Claims 21-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over NINDS, 1995 in view of Bundick et al, 1992 (IDS) and Mori et al, 1997 and further in view of Sharkey et al, 1994 or Kelly et al, 1997 (IDS) as evidenced by Steiner et al, 1998 and further in view of Meden et al, 1993 and Hantson et al, 1997. The teaching of the combination of NINDS, Bundick et al, Mori et al, 1997, Sharkey et al, Kelly et al, and Steiner et al are described in the prior action and summarized in (1) above. Said combination of references does not specifically teach treatment with a neuroprotectant and a thrombolytic within three hours or administration simultaneously or sequentially. However, Steiner et al states that the FDA has approved t-PA for treatment only within three hours of an acute stroke (pg 2, parg 2). Therefore, it would be obvious to a person of ordinary skill in the art to administer t-PA and a neuroprotectant within three hours. Furthermore, Meden et al, 1993 teach that combination therapy with t-PA and a

neuroprotectant is effective if given within two hours of stroke (Table 1). The limitations recited in Claims 23-26, of administering t-PA and a neuroprotectant simultaneously or sequentially, are taught by Hantsen et al, 1997 (Abstract; pg 1, lines 1-3). Therefore, Claims 21-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over NINDS, 1995 in view of Bundick et al, 1992 (IDS) and Mori et al, 1997 and further in view of Sharkey et al, 1994 or Kelly et al, 1997 (IDS) as evidenced by Steiner et al, 1998 and further in view of Meden et al, 1993 and Hantson et al, 1997.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sheridan L. Swope whose telephone number is 571-272-0943. The examiner can normally be reached on M-F; 9:30-7 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached on 571-272-0928. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Sheridan Lee Swope, Ph.D.

REBECCA E. PROUTY
PRIMARY EXAMINER
GROUP 1600
1600

Utility

The following is an examiner's statement of reasons for allowance:

All elected Claims, XXXX, are limited to methods for treating XXX using the combination of XX and XX. The utility of said methods as a treatment for XXX, is credible based on the fact that the combination of FK506 and t-PA cause a 23% reduction of ischemic brain damage in the MCA model of *in vivo* thrombotic occlusion (Example 1, pg 15, parg 3-pg 17, parg 2)